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I.V. MIDAZOLAM AS AN INDUCTION AGENT FOR ANAESTHESIA: A STUDY IN VOLUNTEERS

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SUMMARY

The central nervous and cardiovascular effects of midazolam 0.15 mg kg^{-1} were studied in 20 healthy, unpremedicated volunteers (10 male and 10 female). No important side-effects were noted and the venous tolerance to midazolam was excellent. Three minutes after injection mean systolic arterial pressure decreased from 121 ± (SEM) 2 mm Hg to 115 ± (SEM) 2 mm Hg and diastolic pressure from 78 ± 2 to 70 ± 2 mm Hg ($P < 0.05$), and these effects persisted for at least 20 min. Heart rate increased from 77 ± 4 beat min^{-1} to 90 ± 3 and 88 ± 3 beat min^{-1} 1 and 3 min after the injection ($P < 0.05$). Anterograde amnesia (40 ± 3 min duration) and drowsiness (lasting 128 ± 23 min) were observed in all subjects. Loss of the eyelash reflex and apnoea were observed more often in the male group than in the female subjects. Midazolam 0.15 mg kg^{-1} was not sufficient to induce anaesthesia reliably in healthy unpremedicated volunteers.

Midazolam (Ro 21-3981), a new water-soluble benzodiazepine which can be used for the induction of anaesthesia, has two important advantages over diazepam: a short duration of action and absence of vascular irritation when administered i.v. (Conner, Katz and Pagano, 1978; Fragen, Gahl and Caldwell, 1978; Reves et al., 1979). The effects of the administration of midazolam i.v. on the central nervous and cardiovascular systems were determined in healthy volunteers and an assessment of the use of this drug as an induction agent for general anaesthesia was made.

SUBJECTS AND METHODS

Twenty volunteers, 10 female and 10 male (mean age 33 ± 1.5 yr (mean ± SEM)), weighing 64.2 ± 1.7 kg were studied. Informed consent was obtained and the committee for ethics in human research of our institution approved the programme. The subjects had neither previous medical problem nor took regular medication or alcohol. Each volunteer was fasted for at least 12 h before the beginning of the study which was undertaken before 10 a.m. A Teflon cannula was inserted in a vein on the dorsum of the left hand and a solution of 5% dextrose 100 ml h^{-1} was administered. The e.c.g. and arterial pressure (cuff on right arm) were monitored.

The subjects rested for 30 min in the supine position, and then systolic and diastolic arterial pressures were measured by auscultation (mean arterial pressure was calculated as diastolic pressure + one-third of the pulse pressure). Heart rate and respiratory frequency were determined also. At time zero midazolam maleate 0.15 mg kg^{-1} in a 0.25% solution was injected i.v. over 15 s and the cannula was flushed using the i.v. infusion while the subject was asked to count aloud. Arterial pressure, heart rate and respiratory frequency were measured again at 1, 3, 5 and 20 min after injection of the drug.

The following observations were noted: time to the onset of dysarthria; time to cessation of counting; time and duration of disappearance of the eyelash reflex; onset and duration of apnoea; time of opening the eyes spontaneously; duration of sleep (time between injection of the drug and the moment at which the subjects remained awake and kept the eyes open without stimulation); duration of subjective drug effect.

Retrograde amnesia, defined as a lack of recall before injection, was tested by showing the volunteer a playing card and a written number 30 s before the administration of the drug. As soon as the subject became rousable, he was asked to state the card and number shown to him before injection.

Anterograde amnesia, defined as a lack of recall after the administration of the drug, was tested by showing a card and a number to the volunteer. As soon as his eyelash reflex had returned he had to identify them aloud. The recall was tested 1 min

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after the initial presentation. This procedure was repeated every 5 min, each time with a different number and card. The time at which the volunteer started to recall was accepted as being the end of anterograde amnesia.

A neurological scoring system (table I) was established to compare the overall effects of midazolam on the central nervous system and the differences between males and females.

TABLE I. *Neurological scoring system. Maximum possible score = 22; minimum possible score = 4*

		Score
(1) Duration of dysarthria	< 30 s	1
	30–60 s	2
	> 60 s	3
(2) Time of cessation of counting	< 100 s	2
	100–300 s	1
	> 300 s	0
(3) Loss of eyelash reflex	yes	2
	no	0
(4) Apnoea	yes	2
	no	0
(5) Duration of closure of eyes	> 10 min	2
	< 10 min	1
	never closed	0
(6) Opening of eyes on command	yes	0
	no	2
(7) Duration of sedation	< 30 min	1
	30–60 min	2
	> 60 min	3
(8) Duration of subjective effect	< 4 h	1
	4–8 h	2
	> 8 h	3
(9) Duration of amnesia	< 30 min	1
	30–45 min	2
	> 45 min	3

Twenty-two minutes after injection of the drug, the volunteer was asked to stand up and walk and his ability was assessed as good, fair or bad. After 60 min, in order to test the subject's concentration, he was asked to read a written text aloud. The reading was assessed good, fair or bad. Twenty-four hours after the experiment, each volunteer had to signify whether the experience had been acceptable, fair or unacceptable. Signs and symptoms of venous irritation were sought at 48 h. Statistical analysis was carried out using the Student's *t* test and the Chi-square test. All data are expressed as mean ± SEM.

RESULTS

The cardiovascular effects of midazolam 0.15 mg kg^{-1} i.v. over 15 s are summarized in figure 1. The systolic

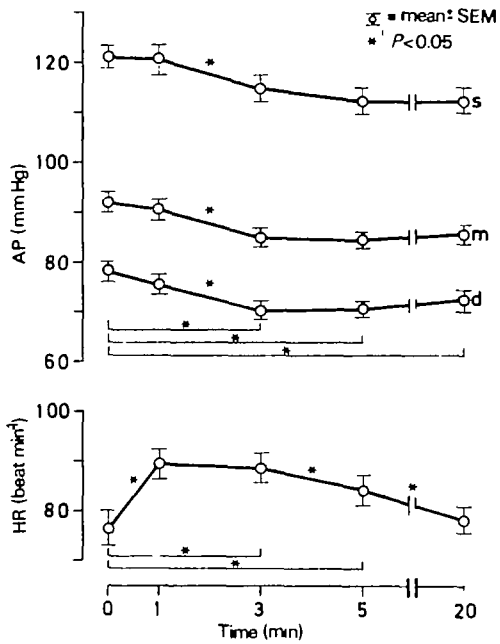

FIG. 1. Variations of systolic (s), mean (m), diastolic (d), arterial pressures (AP) and heart rate (HR) after i.v. injection of midazolam maleate 0.15 mg kg^{-1} in 20 healthy volunteers.

and diastolic arterial pressures decreased 3 min after the injection from 121 ± 2 to 115 ± 2 mm Hg and 78 ± 2 to 70 ± 2 mm Hg respectively ($P < 0.05$). These decreases in arterial pressure remained constant for at least 20 min. The heart rate increased 1 min after the administration of the drug, from 77 ± 4 to 90 ± 3 beat min^{-1} ($P < 0.05$) and lasted for 5 min. When the subjects were asked to stand up 22 min after the injection, the mean arterial pressure did not change significantly (86 ± 2 to 82 ± 2 mm Hg), whereas the heart rate increased from 78 ± 3 to 89 ± 3 beat min^{-1} ($P < 0.05$).

The effects of midazolam on the central nervous system are summarized in figure 2. All time data are related to the time of beginning the injection. Dysarthria occurred in all volunteers, at a mean time of 49 ± 4 s after injection. Seventeen of the 20 subjects stopped counting at 120 ± 22 s; the remaining three continued counting for more than 5 min. Ten of the 20 subjects (seven male and three female) lost the eyelash reflex at 164 ± 42 s, for a duration of 304 ± 104 s. We observed no retrograde amnesia; every volunteer remembered the card and number shown to him before the injection. However, anterograde amnesia of 40 ± 3 min duration occurred in all

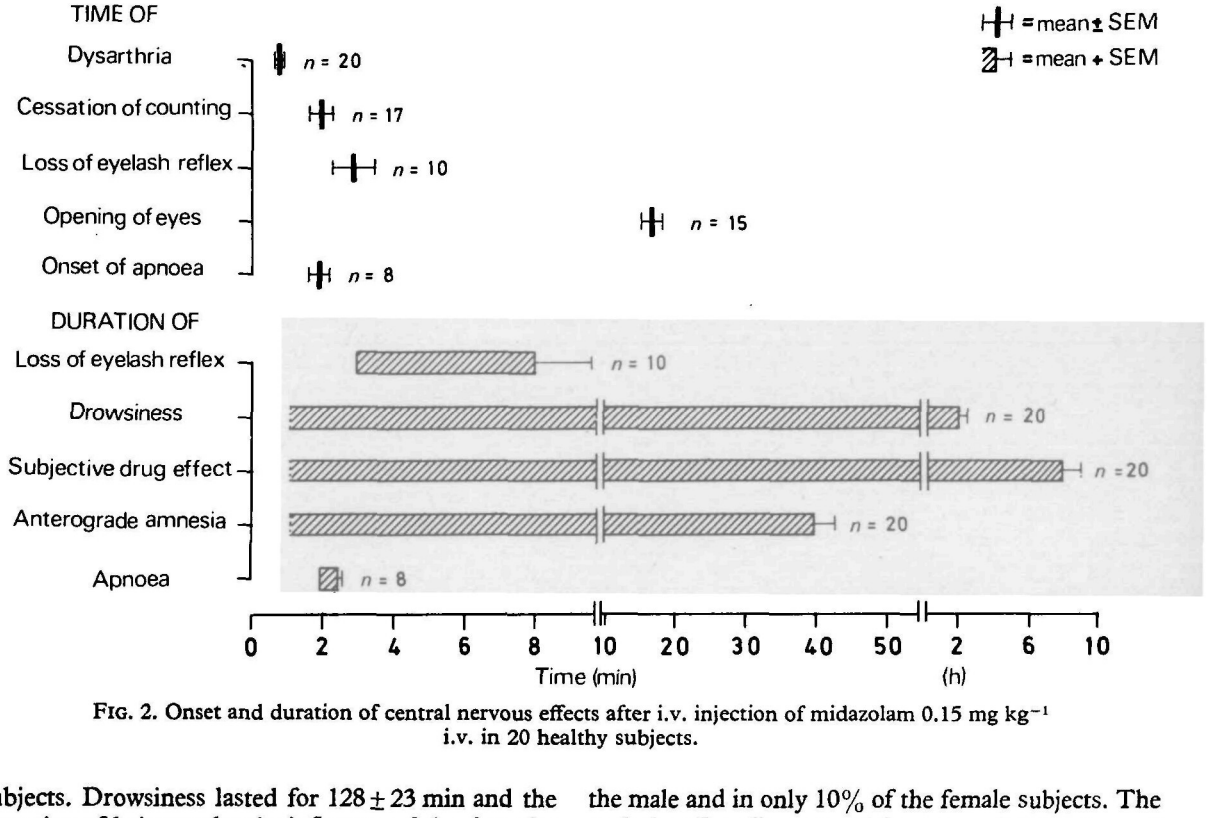

FIG. 2. Onset and duration of central nervous effects after i.v. injection of midazolam 0.15 mg kg^{-1} i.v. in 20 healthy subjects.

subjects. Drowsiness lasted for 128 ± 23 min and the sensation of being under the influence of the drug for 6.7 ± 0.8 h. These symptoms were experienced by every subject. Apnoea occurred in seven of the 10 males and only in one female at 114 ± 19 s and lasted for 30 ± 4 s. Fifteen of the 20 volunteers opened the eyes spontaneously 17 ± 2 min after the administration of the drug.

The effects of the drug were said to be acceptable by 12 of the 20 volunteers and fair by eight others. Twenty-two minutes after the injection, steadiness (walking test) was fair in 12 volunteers and good in eight others. Diplopia occurred in half of the subjects and lasted for about 20 min. After 1 h concentration (reading test) was bad in four subjects, fair in four and good in the other 12. A mild burning at the injection site was noted on three occasions, but no signs or symptoms of venous irritation could be found at 48 h.

Males and females responded differently to the administration of midazolam (fig. 3). The duration of anterograde amnesia was 46 ± 5 min in males and 33 ± 3 min in females. The sensation of being under the influence of the drug lasted for 8 ± 1 h in males and 5.3 ± 1 h in females; apnoea occurred in 70% of the male and in only 10% of the female subjects. The eyelash reflex disappeared in seven of 10 males and three of 10 females. Nine of 10 males closed the eyes after the administration of the drug and reopened them spontaneously after 20 ± 3 min, whereas six of 10 females closed them and reopened them after 12 ± 3 min. The differences in these data between male and female subjects are statistically and clinically significant. If the overall effects on the central nervous system are compared between males and females using the neurological score (table I), the male group had a significantly greater score (16.6 ± 1.1) than the female group (11.0 ± 1.0).

DISCUSSION

The present study shows that midazolam 0.15 mg kg^{-1} produced drowsiness and amnesia in all healthy young volunteers examined. Other effects on the central nervous system were not observed repeatedly (fig. 2). There was no retrograde amnesia, but anterograde amnesia similar to that produced by diazepam (Dundee and Haslett, 1970) was impressive since none of the subjects remembered standing up and walking 22 min after the injection. The loss of the

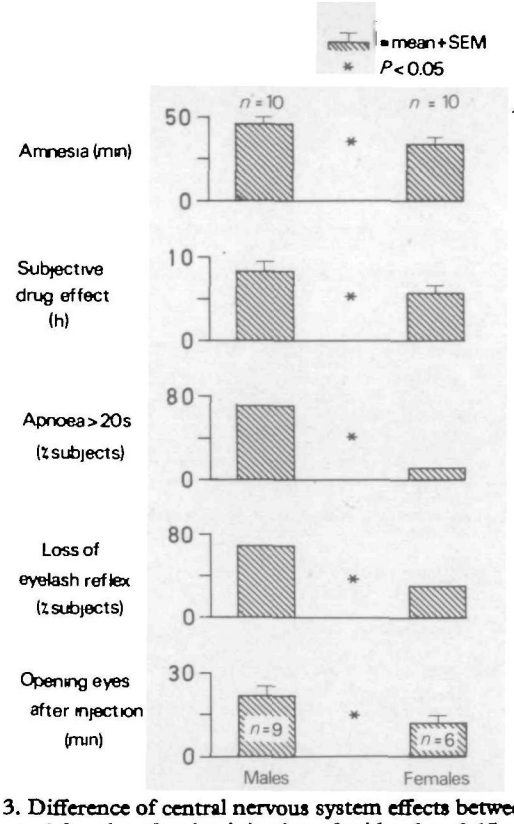

FIG. 3. Difference of central nervous system effects between males and females after i.v. injection of midazolam 0.15 mg kg^{-1} i.v.

eyelash reflex, a useful sign during the induction of anaesthesia, was observed in only 50% of the subjects. These data confirm those of Reves, Corssen and Holcomb (1978) and suggest that midazolam 0.15 mg kg^{-1} is inadequate to induce anaesthesia reliably in unpremedicated young subjects. It has been shown that a larger dose (0.2 mg kg^{-1}) provides a satisfactory induction of anaesthesia in 100% of unpremedicated patients (Reves, Corssen and Holcomb, 1978).

Our study shows that the i.v. administration of midazolam 0.15 mg kg^{-1} produces a statistically significant but clinically unimportant decrease in arterial pressure and an increase in heart rate in healthy volunteers. Other investigations in older but healthy patients confirm our findings (Conner, Katz and Pagano, 1978; Fragen, Gahl and Caldwell, 1978). At larger doses or in patients specially at risk midazolam could possibly cause a greater cardiovascular disturbance.

The difference in the sensitivity to midazolam between males and females was significant for five important neurological indices (fig. 3) and it was confirmed by the neurological scoring system applied. Our study does not provide data to explain this difference. It could be the result of a true decreased sensitivity to midazolam or of an increased volume of distribution in female subjects. This difference requires investigation and confirmation by further studies.

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ADMINISTRATION DE MIDAZOLAM PAR VOIE INTRAVEINEUSE EN TANT QU'AGENT D'INDUCTION DE L'ANESTHESIE: ETUDE EFFECTUEE SUR DES VOLONTAIRES

RESUME

On a étudié sur 20 volontaires (10 hommes et 10 femmes) en bonne santé, n'ayant reçu aucune prémédication, les effets de 0,15 mg kg^{-1} de midazolam sur le système nerveux central et sur le système cardiovasculaire. On n'a remarqué aucun effet secondaire important et la tolérance veineuse au midazolam a été excellente. Trois minutes après l'injection, la pression systolique artérielle moyenne a baissé de 121 mm Hg $\pm$ 2 (écart type des moyennes) à 115 mm Hg $\pm$ 2 (écart type des moyennes) et la pression diastolique a diminué de 78 mm Hg $\pm$ 2 à 70 mm Hg $\pm$ 2 ($P < 0{,}05$) et ces effets se sont maintenus pendant au moins 20 min. La fréquence cardiaque a augmenté de 77 battements $min^{-1} \pm 4$ à 90 ± 3 et 88 ± 3 battements min^{-1}; 1 et 3 min après l'injection ($P < 0{,}05$). On a constaté sur tous les sujets une amnésie antérograde (d'une durée de 40 min $\pm$ 3 min) et une somnolence diurne (durant 128 min $\pm$ 23 min). On a observé plus souvent sur le groupe d'hommes que sur le groupe de femmes la perte du réflexe de cillement et de

l'apnée. Le midazolam administré à raison de 0,15 mg kg^{-1} n'a pas été suffisant pour induire l'anesthésie d'une manière fiable à des volontaires en bonne santé n'ayant reçu aucune prémédication.

INTRAVENÖSES MIDAZOLAM ZUR NARKOSEEINLEITUNG: EINE STUDIE AN FREIWILLIGEN

ZUSAMMENFASSUNG

Die Zentralnerven- und Kardiovaskulärreffekte von 0,15 mg kg^{-1} Midazolam wurden an 20 gesunden, nicht vorbehandelten Friewilligen (10 männlich, 10 weiblich) studiert. Keine wichtigen Nebenerscheinungen wurden bemerkt, und die venöse Toleranz auf die Droge war ausgezeichnet. Drei Minuten nach der Injektion sank der systolische Arteriendruck von 121± (SEM) 2 mm Hg auf 115± (SEM) 2 mm Hg, und der diastolische Druck von 78±2 auf 70±2 auf 70±2 mm Hg ($P<0,05$), und diese Effekte dauerten wenigstens 20 min an. Pulszahl stieg von 77±4 auf 90±3 und auf 88±3 Schläge min^{-1} 1 und 3 Minuten nach der Injektion ($P<0,05$). Anterograde Amnesie (40±3 min Dauer) und Schläfrigkeit (Dauer 128±23 min) wurden bei allen Personen beobachtet. Verlust des Lidreflexes und Apnoe wurden bei den Männern häufiger als bei den Frauen beobachtet. Midazolam in Höhe von 0,15 mg kg^{-1} war nicht ausreichend, um bei gesunden, nicht vorbehandelten Freiwilligen Narkose einzuleiten.

MIDAZOLAM INTRAVENOSA CUAL UN AGENTE DE INDUCCION DE ANESTESIA: UN ESTUDIO EFECTUADO CON VOLUNTARIOS

SUMARIO

Se estudiaron los efectos cardiovasculares y sobre el sistema nervioso central, de 0,15 mg kg^{-1} de midazolam en 20 voluntarios sanos y sin previa medicación (10 hombres y 10 mujeres). No se apreciaron efectos secundarios importantes y la tolerancia venosa al midazolam fue excelente. Tres minutos después de la inyección la presión sistólica arterial disminuyó desde 121±2 mm Hg hasta 115±2 mm Hg y la presión diastólica disminuyó desde 78±2 mm Hg hasta 70±2 mm Hg ($P<0,05$) y estos efectos perduraron durante, por lo menos, 20 minutos. El rítmo cardiaco aumentó desde 77±4 latidos min^{-1} hasta 90±3 y 88±3 latidos min^{-1}, 1 y 3 min después de la inyección ($P<0,05$). En todos los sujetos se observó amnesia de anterogrado (40±3 min de duración) y adormecimiento (durante 128±23 min). En el grupo de hombres se observó apnea y pérdida de reflejo en el párpado con más frecuencia que en las mujeres. No fueron suficientes 0,15 mg kg^{-1} de midazolam para inducir una anestesia fiable en voluntarios sanos y sin previa medicación.